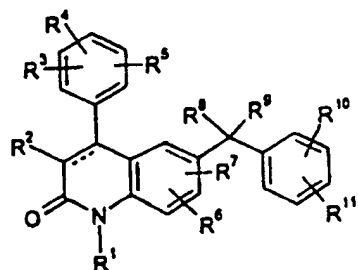




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(54) Title: QUINOLIN-2-ONE DERIVATIVES USEFUL AS ANTICANCER AGENTS



(1)

## (57) Abstract

Compounds of formula (1) and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein  $R^8$  is H,  $-OR^{12}$ ,  $-NR^{12}R^{13}$ ,  $-NR^{12}C(O)R^{13}$ , cyano,  $-C(O)OR^{13}$ ,  $-SR^{12}$ ,  $-(CR^{13}R^{14})_t$  (4-10 membered heterocyclic), wherein  $t$  is an integer from 0 to 5, or  $C_1-C_6$  alkyl, wherein said heterocyclic and alkyl moieties are optionally substituted by 1 to 3  $R^6$  substituents;  $R^9$  is  $-(CR^{13}R^{14})_t$  (imidazolyl) wherein  $t$  is an integer from 0 to 5 and said imidazolyl moiety is optionally substituted by 1 or 2  $R^6$  substituents; provided that where  $R^1$  is not  $-(CR^{13}R^{14})_t$  ( $C_3-C_{10}$  cycloalkyl), wherein  $t$  is an integer from 0 to 5, then  $R^8$  is triazolyl optionally substituted by 1 or 2  $R^6$  groups, or at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $-CH=NOR^{12}$  or  $-S(O)_jR^{12}$  wherein  $j$  is an integer from 0 to 2. The compounds of formula (1) are useful in the treatment of hyperproliferative disorders, such as cancer, in mammals. The invention also relates to pharmaceutical compositions containing the compounds of formula (1) and to methods of inhibiting abnormal cell growth, including cancer, in a mammal by administering the compounds of formula (1) to a mammal requiring such treatment.

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QUINOLIN-2-ONE DERIVATIVES USEFUL AS ANTICANCER AGENTSBackground of the Invention

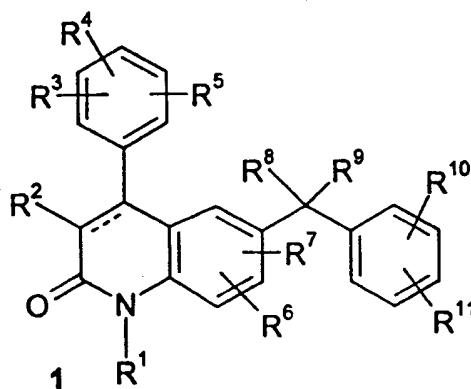
This invention relates to a series of quinolin-2-one derivatives that are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as agents to combat tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., *Science*, Vol. 260, 1834 to 1837, 1993). The compounds of the present invention exhibit activity as inhibitors of the enzyme farnesyl protein transferase and are therefore believed to be useful as anti-cancer and anti-tumor agents. Further, the compounds of the present invention may be active against any tumors that proliferate by virtue of farnesyl protein transferase.

Summary of the Invention

The present invention relates to compounds of formula 1



30

and to pharmaceutically acceptable salts, prodrugs and solvates thereof wherein:

the dashed line indicates that the bond between C-3 and C-4 of the quinolin-2-one ring is a single or double bond;

5  $R^1$  is selected from H,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{13}R^{14})_qC(O)R^{12}$ ,  $-(CR^{13}R^{14})_qC(O)OR^{15}$ ,  $-(CR^{13}R^{14})_qOR^{12}$ ,  $-(CR^{13}R^{14})_qSO_2R^{15}$ ,  $-(CR^{13}R^{14})_t(C_3$ - $C_{10}$  cycloalkyl),  $-(CR^{13}R^{14})_t(C_6$ - $C_{10}$  aryl), and  $-(CR^{13}R^{14})_t$ (4-10 membered heterocyclic), wherein  $t$  is an integer from 0 to 5 and  $q$  is an integer from 1 to 5, said cycloalkyl, aryl and heterocyclic  $R^1$  groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  saturated cyclic group, or a 4-10 membered heterocyclic group; and  
 10 the foregoing  $R^1$  groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4  $R^6$  groups;

$R^2$  is halo, cyano,  $-C(O)OR^{15}$ , or a group selected from the substituents provided in the definition of  $R^{12}$ ;

each  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  is independently selected from H,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido,  $-OR^{12}$ ,  $-C(O)R^{12}$ ,  $-C(O)OR^{12}$ ,  $-NR^{13}C(O)OR^{15}$ ,  $-OC(O)R^{12}$ ,  $-NR^{13}SO_2R^{15}$ ,  $-SO_2NR^{12}R^{13}$ ,  $-NR^{13}C(O)R^{12}$ ,  $-C(O)NR^{12}R^{13}$ ,  $-NR^{12}R^{13}$ ,  $-CH=NOR^{12}$ ,  $-S(O)_jR^{12}$  wherein  $j$  is an integer from 0 to 2,  $-(CR^{13}R^{14})_t(C_6$ - $C_{10}$  aryl),  $-(CR^{13}R^{14})_t$ (4-10 membered heterocyclic), and  $-(CR^{13}R^{14})_t(C_3$ - $C_{10}$  cycloalkyl), and wherein in the foregoing  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  groups  $t$  is an integer from 0 to  
 15 5; the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido,  $-NR^{13}SO_2R^{15}$ ,  $-SO_2NR^{12}R^{13}$ ,  $-C(O)R^{12}$ ,  $-C(O)OR^{12}$ ,  $-OC(O)R^{12}$ ,  
 20  $-NR^{13}C(O)OR^{15}$ ,  $-NR^{13}C(O)R^{12}$ ,  $-C(O)NR^{12}R^{13}$ ,  $-NR^{12}R^{13}$ ,  $-OR^{12}$ ,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $-(CR^{13}R^{14})_t(C_6$ - $C_{10}$  aryl), and  $-(CR^{13}R^{14})_t$ (4-10 membered heterocyclic), wherein  $t$  is an integer from 0 to 5;

$R^8$  is H,  $-OR^{12}$ ,  $-NR^{12}R^{13}$ ,  $-NR^{12}C(O)R^{13}$ , cyano,  $-C(O)OR^{13}$ ,  $-SR^{12}$ ,  $-(CR^{13}R^{14})_t$ (4-10 membered heterocyclic), wherein  $t$  is an integer from 0 to 5, or  $C_1$ - $C_6$  alkyl, wherein said  
 30 heterocyclic and alkyl moieties are optionally substituted by 1 to 3  $R^6$  substituents;

$R^9$  is  $-(CR^{13}R^{14})_t$ (imidazolyl) wherein  $t$  is an integer from 0 to 5 and said imidazolyl moiety is optionally substituted by 1 or 2  $R^6$  substituents;

each  $R^{10}$  and  $R^{11}$  is independently selected from the substituents provided in the definition of  $R^6$ ;

35 each  $R^{12}$  is independently selected from H,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{13}R^{14})_t(C_3$ - $C_{10}$  cycloalkyl),  $-(CR^{13}R^{14})_t(C_6$ - $C_{10}$  aryl), and  $-(CR^{13}R^{14})_t$ (4-10 membered heterocyclic), wherein  $t$  is an integer from 0 to 5; said cycloalkyl, aryl and heterocyclic  $R^{12}$  groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing  $R^{12}$  substituents, except H, are optionally substituted by 1 to 3 substituents  
 40 independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido,  $-C(O)R^{13}$ ,  $-C(O)OR^{13}$ ,  $-OC(O)R^{13}$ ,  $-NR^{13}C(O)R^{14}$ ,  $-C(O)NR^{13}R^{14}$ ,  $-NR^{13}R^{14}$ , hydroxy,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_{10}$  alkenyl and  $C_1$ - $C_6$  alkoxy;

5 each  $R^{13}$  and  $R^{14}$  is independently H or  $C_1$ - $C_6$  alkyl, and where  $R^{13}$  and  $R^{14}$  are as  $-(CR^{13}R^{14})_q$  or  $(CR^{13}R^{14})_t$ , each is independently defined for each iteration of q or t in excess of 1;

$R^{15}$  is selected from the substituents provided in the definition of  $R^{12}$  except  $R^{15}$  is not H; and,

10 provided that where  $R^1$  is not  $-(CR^{13}R^{14})_t(C_3$ - $C_{10}$  cycloalkyl), wherein t is an integer from 0 to 5, optionally substituted as provided in the definition of  $R^1$  above, then  $R^8$  is triazolyl optionally substituted by 1 or 2  $R^6$  groups, or at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $-CH=NOR^{12}$  or  $-S(O)_jR^{12}$  wherein j is an integer from 0 to 2 and  $R^{12}$  is as defined above.

Preferred compounds of formula 1 include those wherein  $R^3$  is  $-CH=NOR^{12}$ . More  
15 preferred compounds include those wherein  $R^1$  is H,  $C_1$ - $C_6$  alkyl, or cyclopropylmethyl;  $R^2$  is H; and  $R^8$  is  $-NR^{12}R^{13}$ ,  $-OR^{12}$ , or a heterocyclic group selected from triazolyl, imidazolyl, pyrazolyl, and piperidinyl, wherein said heterocyclic group is optionally substituted by an  $R^6$  group. Even more preferred are those compounds wherein  $R^9$  is imidazolyl optionally substituted by  $C_1$ - $C_6$  alkyl;  $R^8$  is hydroxy, amino, or triazolyl;  $R^1$  is cyclopropylmethyl; and  $R^4$ ,  $R^5$ ,  $R^{10}$  and  $R^{11}$  are each  
20 independently selected from H and halo.

Other preferred compounds formula 1 include those wherein  $R^1$  is cyclopropylmethyl. More preferred compounds include those wherein  $R^2$  is H; and  $R^8$  is  $-NR^{12}R^{13}$ ,  $-OR^{12}$ , or a heterocyclic group selected from triazolyl, imidazolyl, pyrazolyl, and piperidinyl, wherein said heterocyclic group is optionally substituted by an  $R^6$  group.

25 Other preferred compounds of formula 1 include those wherein  $R^8$  is triazolyl optionally substituted by an  $R^6$  group. More preferred compounds include those wherein  $R^1$  is H,  $C_1$ - $C_6$  alkyl, or cyclopropylmethyl;  $R^2$  is H;  $R^9$  is imidazolyl optionally substituted by  $C_1$ - $C_6$  alkyl; and  $R^4$ ,  $R^5$ ,  $R^{10}$  and  $R^{11}$  are each independently selected from H and halo.

Specific preferred compounds include the following:

30 3-{6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl}-benzaldehyde O-methyl-oxime;

3-{6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl}-benzaldehyde O-ethyl-oxime;

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-  
35 1-cyclopropylmethyl-1H-quinolin-2-one;

6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one;

40 and the pharmaceutically acceptable salts, prodrugs and solvates of the foregoing compounds, as well as stereoisomers of the foregoing compounds.

5           This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting farnesyl protein transferase. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone  
10 cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the  
15 endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary  
20 adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

          This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a  
25 compound of the formula 1, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in treating abnormal cell growth.

          This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt or solvate thereof, in combination  
30 with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

          The present invention also relates to a method for the treatment of an infection in a mammal, including a human, that is facilitated by farnesyl protein transferase, such as hepatitis  
35 delta virus or malaria, which comprises administering to said mammal a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt or solvate thereof.

          This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of  
40 the formula 1, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting farnesyl protein transferase, and a pharmaceutically acceptable carrier. In

5 one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the  
10 vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis,  
15 neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

20 This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the treatment of  
25 abnormal cell growth in a mammal, including a human, which comprises a therapeutically effective amount of a compound of formula 1, as defined above, or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes,  
30 topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

This invention also relates to a pharmaceutical composition for the treatment of an infection in a mammal, including a human, that is facilitated by farnesyl protein transferase, such as malaria or hepatitis delta virus, comprising an amount of a compound of the formula 1, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in  
35 treating abnormal cell growth, and a pharmaceutically acceptable carrier.

"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation  
40 in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs; and (4) any tumors that proliferate by virtue of farnesyl protein transferase.

5       The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

10       The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

      The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties.

      The term "cycloalkyl", as used herein, unless otherwise indicated, includes cyclic alkyl  
15       moieties wherein alkyl is as defined above.

      The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above.

      The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

20       The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

      The term "4-10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms, generally 1 to 4 heteroatoms, each selected from O, S and N, wherein each heterocyclic group  
25       has from 4-10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or more oxo moieties. An example of a 4 membered heterocyclic group is azetidiny (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl  
30       and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinoliziny. Examples of aromatic heterocyclic groups are pyridiny, imidazolyl, pyrimidiny, pyrazolyl, triazolyl, pyraziny, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl,  
35       isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnoliny, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridiny, puriny, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazoliny,

40



5 quinoxaliny, naphthyridiny, and furopyridiny. The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

Where  $R^{13}$  and  $R^{14}$  are as  $(CR^{13}R^{14})_q$  or  $(CR^{13}R^{14})_t$ , each is independently defined for each iteration of  $q$  or  $t$  in excess of 1. This means, for instance, that where  $q$  or  $t$  is 2 alkylene  
10 moieties of the type  $-CH_2CH(CH_3)-$ , and other asymmetrically branched groups, are included.

The term "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups that may be present in the compounds of formula 1. For example, pharmaceutically acceptable salts include sodium, calcium and potassium salts of carboxylic acid groups and hydrochloride salts of amino groups. Other  
15 pharmaceutically acceptable salts of amino groups are hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. The preparation of such salts is described below.

The subject invention also includes isotopically-labelled compounds, and the  
20 pharmaceutically acceptable salts thereof, which are identical to those recited in formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as  $^2H$ ,  $^3H$ ,  $^{13}C$ ,  
25  $^{14}C$ ,  $^{15}N$ ,  $^{18}O$ ,  $^{17}O$ ,  $^{35}S$ ,  $^{18}F$ , and  $^{36}Cl$ , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as  $^3H$  and  $^{14}C$  are  
30 incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,  $^3H$ , and carbon-14, i.e.,  $^{14}C$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e.,  $^2H$ , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in  
35 some circumstances. Isotopically labelled compounds of formula 1 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses pharmaceutical compositions containing and methods  
40 of treating bacterial infections through administering prodrugs of compounds of the formula 1. Compounds of formula 1 having free amino, amido, hydroxy or carboxylic groups can be

5 converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula 1. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-  
10 hydroxyproline, hydroxylysine, demosine, isodemossine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. The amide and ester moieties may incorporate  
15 groups including but not limited to ether, amine and carboxylic acid functionalities. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in D. Fleisher, R. Bong, B.H. Stewart, Advanced Drug Delivery Reviews (1996) 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs and sulfate  
20 esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in R.P. Robinson et al., J. Medicinal Chemistry (1996) 39, 10.

25 Certain compounds of formula 1 may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula 1, and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula 1, the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. In particular,  
30 the carbon to which the  $R^8$  and  $R^9$  groups are attached represents a potential chiral center; the present invention encompasses all stereoisomers based on this chiral center. The compounds of formula 1 may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof. Certain compounds of formula 1 may also include oxime moieties, such as where  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  or  $R^7$  is  $-CH=NOR^{12}$ , that exist in E or Z configurations. The present  
35 invention includes racemic mixtures of compounds of formula 1 that include such oxime moieties or specific E or Z isomers of such compounds.

#### Detailed Description of the Invention

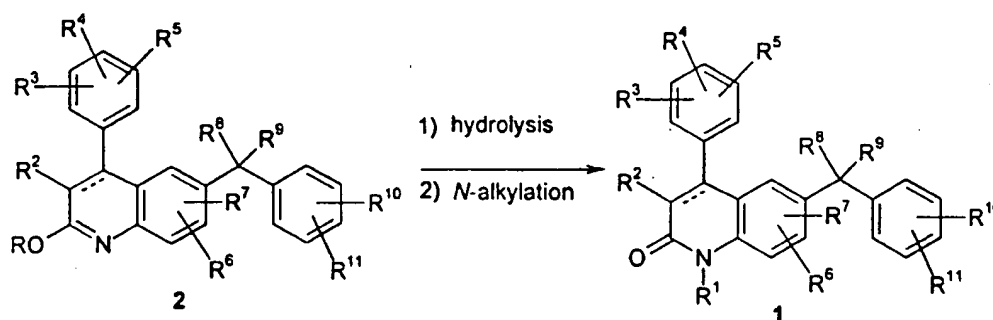
The compounds of formula 1 may be prepared as described below.

40 With reference to Scheme 1 below, the compounds of formula 1 may be prepared by hydrolysing an intermediate ether of formula 2, wherein R is  $C_1$ - $C_6$  alkyl, according to methods

5 familiar to those skilled in the art, such as by stirring the intermediate of formula 2 in an aqueous acid solution. An appropriate acid is, for example, hydrochloric acid. The resulting quinolinone of formula 1 wherein R<sup>1</sup> is hydrogen may be transformed into a quinolinone wherein R<sup>1</sup> has a meaning as defined above apart from hydrogen by *N*-alkylation methods familiar to those skilled in the art.

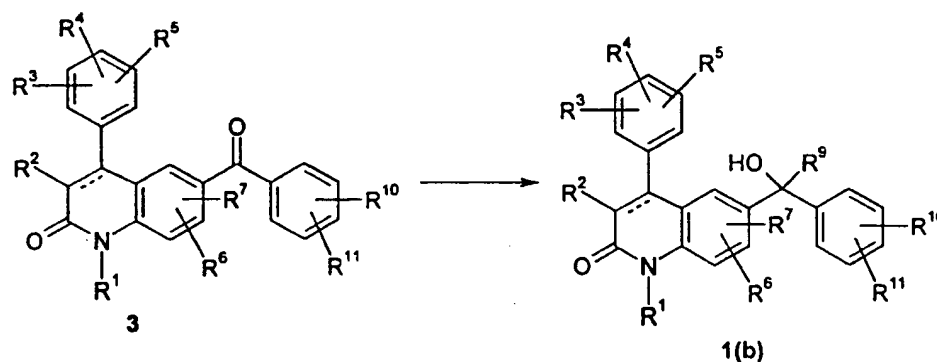
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Scheme 1



With reference to Scheme 2 below, the compounds of formula 1(b), which are compounds of formula 1 wherein R<sup>8</sup> is hydroxy, may be prepared by reacting an intermediate ketone of formula 3 with an intermediate of the formula H-R<sup>9</sup>, wherein R<sup>9</sup> is as defined above and wherein in the imidazolyl moiety of said R<sup>9</sup> group a free nitrogen atom may be protected with an optional protective group, such as a sulfonyl group (for example, a dimethylamino sulfonyl group) which can be removed after the addition reaction. Said reaction requires the presence of a suitable strong base, such as *sec*-butyl lithium, in an appropriate solvent, such as tetrahydrofuran, and the presence of an appropriate silane derivative, such as chloro-*tert*-butyldimethylsilane. The silyl group can be removed with a fluoride source such as tetrabutyl ammonium fluoride. Other procedures with protective groups analogous to silane derivatives can also be applied.

Scheme 2

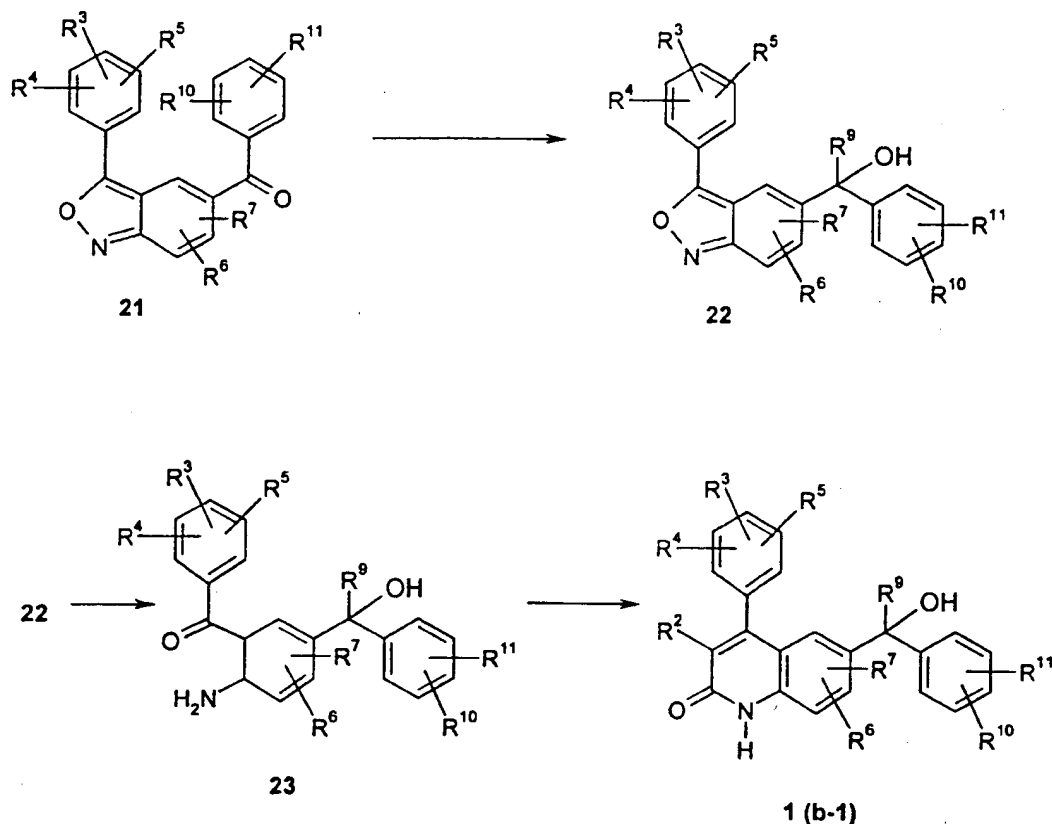


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With reference to Scheme 3 below, compounds of formula 1(b-1), which are compounds of formula 1 wherein the dotted line is a bond and R<sup>1</sup> is hydrogen, can be prepared by reacting an intermediate of formula 21 with an intermediate of formula H-R<sup>9</sup>,

- 5 wherein  $R^9$  is as described above. The resulting intermediate of formula **22** undergoes ring opening of the isoxazole moiety by stirring it with an acid, such as  $TiCl_3$ , in the presence of water. Subsequent treatment of the resulting intermediate of formula **23** with a suitable reagent, such as  $R^2CH_2COCl$  or  $R^2CH_2COOC_2H_5$ , wherein  $R^2$  is as defined above, yields either directly a compound of formula **1(b-1)** or an intermediate which can be converted to a
- 10 compound of formula **1(b-1)** by treatment with a base, such as potassium *tert*-butoxide.

Scheme 3

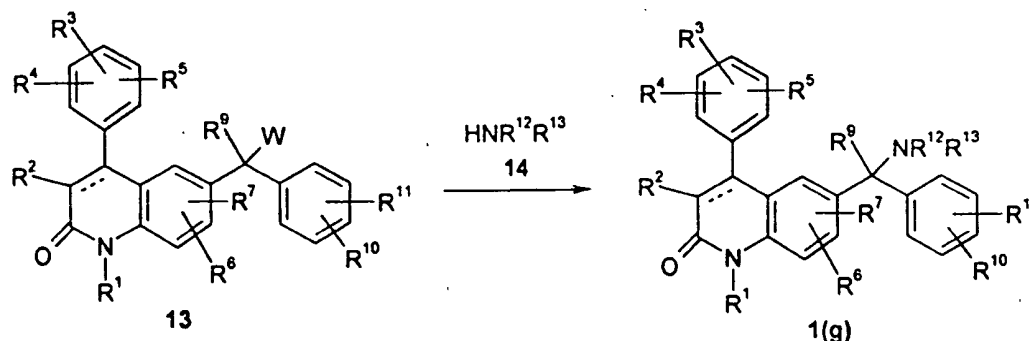


Intermediates of formula **21** can be prepared by treating an intermediate of formula **16**, referred to below with respect to Scheme 9, under acidic conditions.

- 15 With reference to Scheme 4 below, compounds of formula **1** wherein  $R^8$  is a radical of formula  $-NR^{12}R^{13}$  wherein  $R^{12}$  and  $R^{13}$  are as described above (said compounds are represented below by formula **1(g)**), may be prepared by reacting an intermediate of formula **13**, wherein W is an appropriate leaving group, such as halo, with a reagent of formula **14**. Said reaction may be performed by stirring the reactants in an appropriate solvent, such as tetrahydrofuran.
- 20

5

Scheme 4

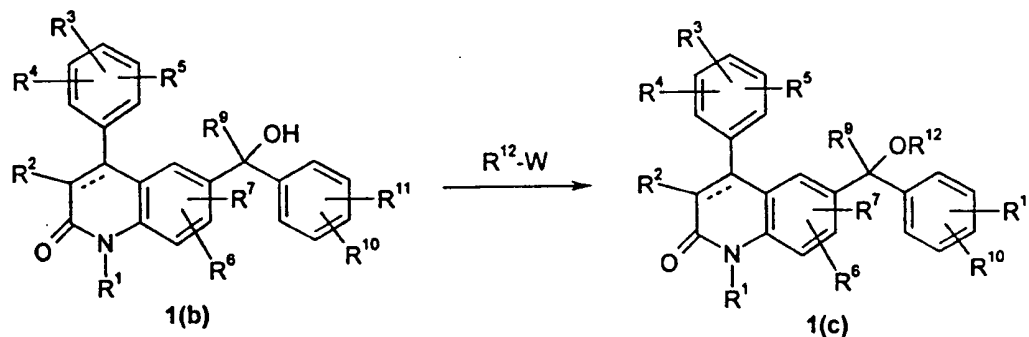


Compounds of formula 1(g), or other embodiments of formula 1, wherein the dotted line represents a bond can be converted into compounds wherein the dotted line does not represent a bond by hydrogenation methods familiar to those skilled in the art. Compounds wherein the dotted line does not represent a bond may be converted into compounds wherein the dotted line represents a bond by oxidation methods familiar to those skilled in the art.

With reference to Scheme 5 below, compounds of formula 1 wherein  $\text{R}^8$  is hydroxy (said compounds being represented by formula 1(b)) may be converted into compounds of formula 1(c), wherein  $\text{R}^{12}$  has the meaning described above except it is not hydrogen, by methods known to those skilled in the art, including O-alkylation or O-acylation reactions; such as by reacting the compound of formula 1(b) with an alkylating reagent such as  $\text{R}^{12}\text{-W}$ , wherein  $\text{R}^{12}$  is as described above, in appropriate conditions, such as in a dipolar aprotic solvent, such as DMF, in the presence of a base, such as sodium hydride.  $\text{W}$  is a suitable leaving group, such as a halo group or a sulfonyl group.

20

Scheme 5



As an alternative to the above reaction procedure, compounds of formula 1(c) may also be prepared by reacting a compound of formula 1(b) with a reagent of formula  $\text{R}^{12}\text{-OH}$ , wherein  $\text{R}^{12}$  is as described above, in acidic medium.

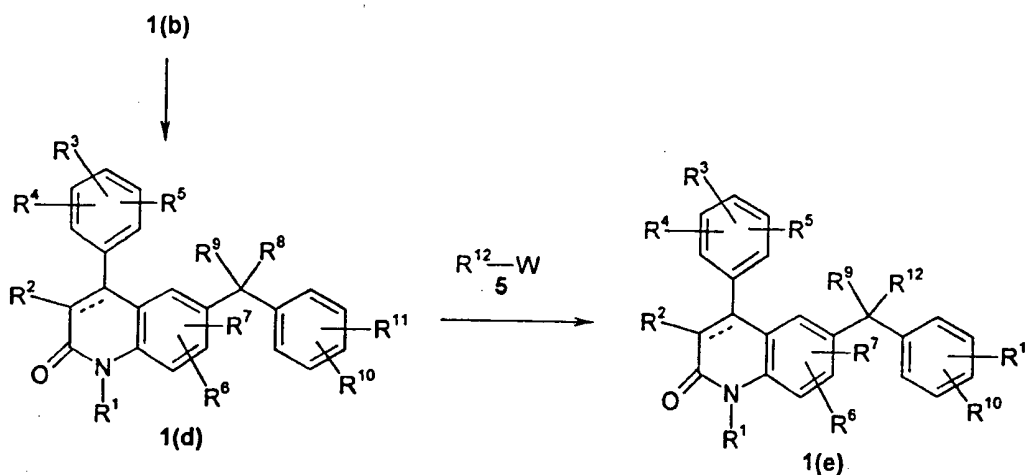
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Compounds of formula 1(b) may also be converted into compounds of formula 1(g), wherein  $\text{R}^{12}$  is hydrogen and  $\text{R}^{13}$  is replaced with  $\text{C}_1\text{-C}_6$  alkylcarbonyl, by reacting compounds of formula 1(b) in acidic medium, such as sulfuric acid, with  $\text{C}_1\text{-C}_6$  alkyl-CN in a Ritter-type

- 5 reaction. Further, compounds of formula 1(b) may also be converted into compounds of formula 1(g), wherein  $R^{12}$  and  $R^{13}$  are hydrogen, by reacting a compound of formula 1(b) with ammonium acetate and subsequent treatment with  $NH_3(aq.)$ .

With reference to Scheme 6 below, compounds of formula 1(b), referred to above, may also be converted into compounds of formula 1(d), wherein  $R^8$  is hydrogen, by submitting  
10 a compound of formula 1(b) to appropriate reducing conditions, such as stirring in trifluoroacetic acid in the presence of an appropriate reducing agent, such as sodium borohydride, or, alternatively, stirring the compound of formula 1(b) in acetic acid in the presence of formamide. Further, the compound of formula 1(d) wherein  $R^8$  is hydrogen may be converted into a compound of formula 1(e) wherein  $R^{12}$  is  $C_1$ - $C_{10}$  alkyl by reacting the  
15 compound of formula 1(d) with a reagent of formula 5, wherein W is an appropriate leaving group, in an appropriate solvent, such as diglyme, in the presence of a base, such as potassium *tert*-butoxide.

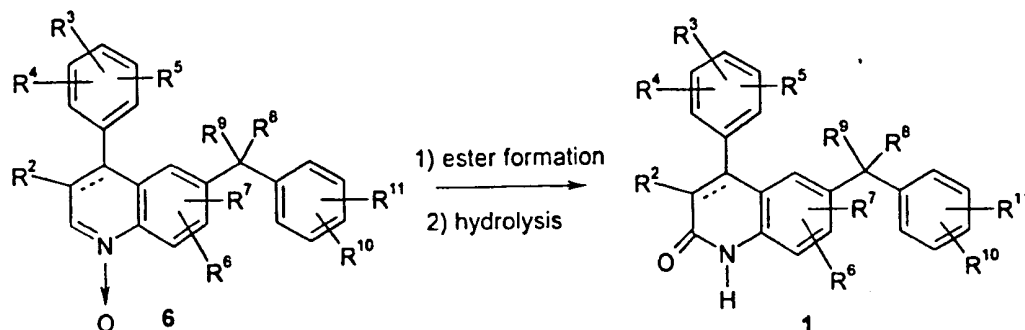
Scheme 6



- 20 With reference to Scheme 7 below, compounds of formula 1 may be prepared by reacting a nitron of formula 6 with the anhydride of a carboxylic acid, such as acetic anhydride, thus forming the corresponding ester on the 2-position of the quinoline moiety. Said quinoline ester can be hydrolyzed *in situ* to the corresponding quinolinone using a base, such as potassium carbonate.

5

Scheme 7



Alternatively, compounds of formula 1 can be prepared by reacting a nitron of formula 6 with a sulfonyl containing electrophilic reagent, such as *p*-toluenesulfonylchloride, in the presence of a base, such as aqueous potassium carbonate. The reaction initially involves the formation of a 2-hydroxy-quinoline derivative which is subsequently tautomerized to the desired quinolinone derivative. The application of conditions of phase transfer catalysis, which are familiar to those skilled in the art, may enhance the rate of the reaction.

Compounds of formula 1 may also be prepared by an intramolecular photochemical rearrangement of compounds of formula 6, referred to above. Said rearrangement can be carried out by dissolving the reagents in a reaction-inert solvent and irradiating at a wavelength of 366 nm. It is advantageous to use degassed solutions and to conduct the reaction under an inert atmosphere, such as oxygen-free argon or nitrogen gas, in order to minimize undesired side reactions or reduction of quantum yield.

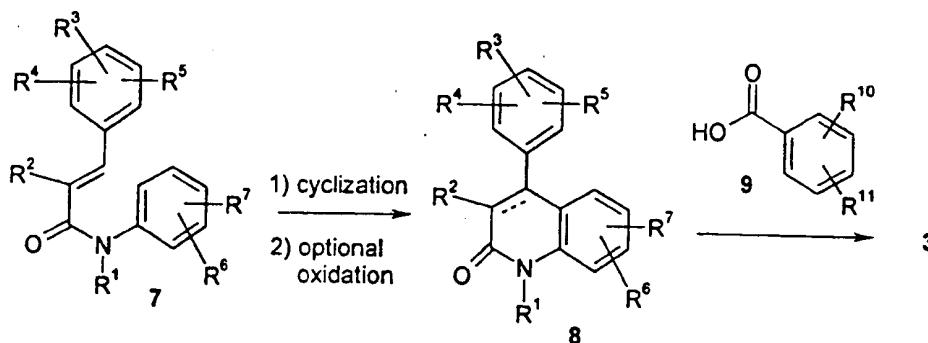
The substituents of the compounds of formula 1 may be converted to other substituents falling within the scope of formula 1 via reactions or functional group transformations familiar to those skilled in the art. A number of such transformations are already described above. Other examples are hydrolysis of carboxylic esters to the corresponding carboxylic acid or alcohol; hydrolysis of amides to the corresponding carboxylic acids or amines; hydrolysis of nitriles to the corresponding amides; amino groups on imidazole or phenyl moieties may be replaced by hydrogen by diazotation reactions familiar to those skilled in the art, and subsequent replacement of the diazo-group by hydrogen; alcohols may be converted into esters and ethers; primary amines may be converted into secondary or tertiary amines; double bonds may be hydrogenated to the corresponding single bond.

With reference to Scheme 8 below, intermediates of formula 3, referred to above, may be prepared by reacting a quinolinone derivative of formula 8 with an intermediate of formula 9, or a functional derivative thereof, under appropriate conditions, such as in the presence of a strong acid (for example, polyphosphoric acid) in an appropriate solvent. The intermediate of formula 8 may be formed by cyclization of an intermediate of formula 7 by stirring in the presence of a strong acid, such as polyphosphoric acid. Optionally, said cyclization reaction

- 5 may be followed by an oxidation step, which can be performed by stirring the intermediate formed after cyclization in an appropriate solvent, such as a halogenated aromatic solvent (for example, bromobenzene), in the presence of an oxidizing agent, such as bromine or iodine. At this stage, the R<sup>1</sup> substituent may be changed to a different moiety by a functional group transformation reaction familiar to those skilled in the art.

10

Scheme 8



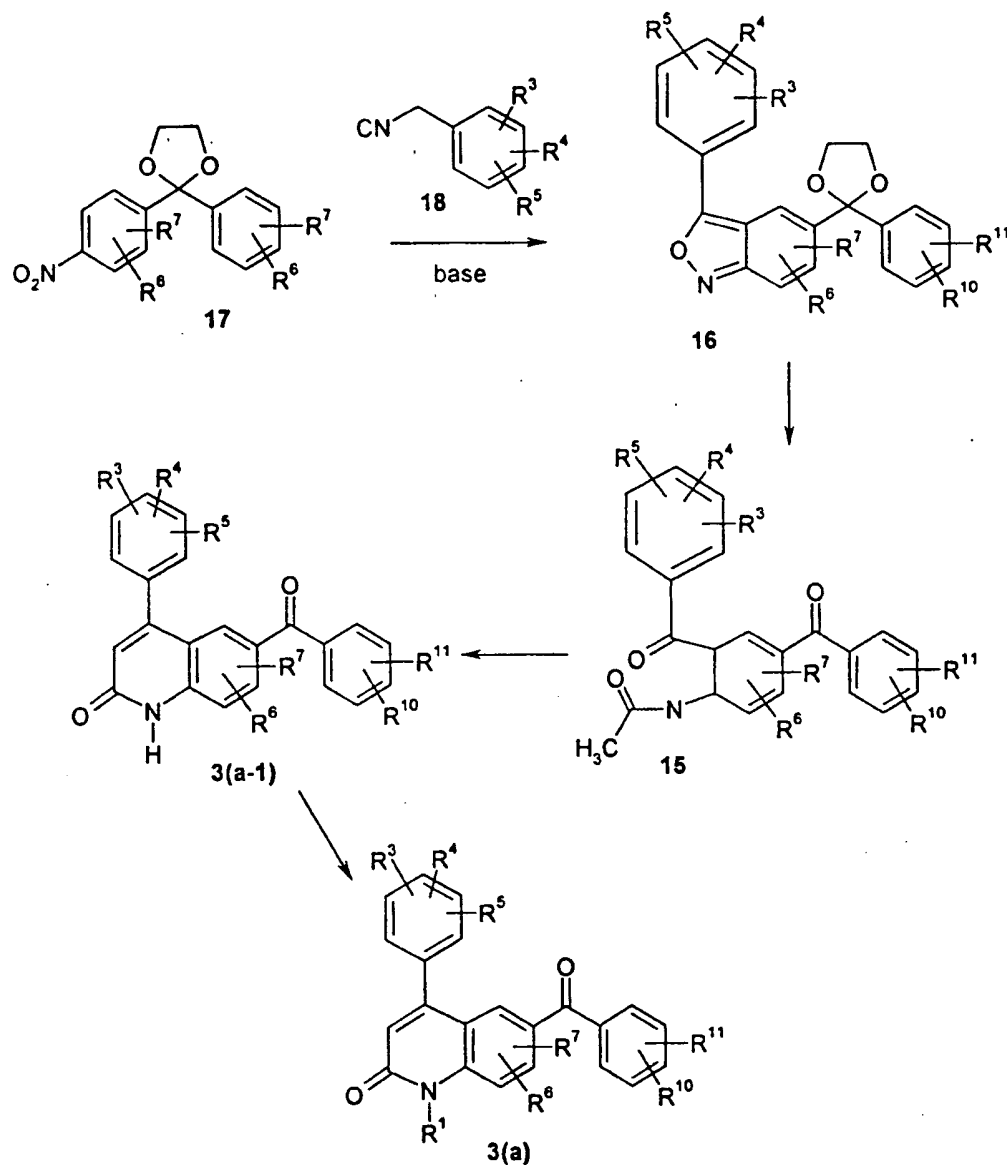
- With reference to Scheme 9 below, intermediates of formula 3(a-1), which are intermediates of formula 3 wherein the dotted line is a bond and R<sup>1</sup> and R<sup>2</sup> are hydrogen, can be prepared starting from an intermediate of formula 17, which is conveniently prepared by protecting the corresponding ketone. Said intermediate of formula 17 is stirred with an intermediate of formula 18 in the presence of a base, such as sodium hydroxide, in an appropriate solvent, such as an alcohol (for example, methanol). The resulting intermediate of formula 16 will undergo hydrolysis of the ketal and ring opening of the isoxazole moiety by stirring the intermediate of formula 16 with an acid, such as TiCl<sub>3</sub>, in the presence of water.
- 15 Subsequently, acetic anhydride can be used to prepare an intermediate of formula 15, which will undergo ring closure in the presence of a base, such as potassium *tert*-butoxide.

- Intermediates of formula 3(a-1) can be converted to intermediates of formula 3(a), which are intermediates of formula 3 wherein the dotted line represents a bond, R<sup>2</sup> is hydrogen, and R<sup>1</sup> is other than hydrogen as defined above, using *N*-alkylation procedures
- 25 familiar to those skilled in the art.



5

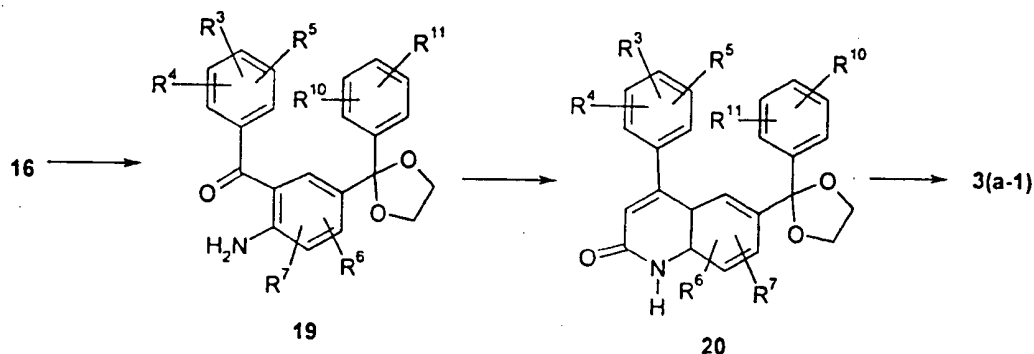
Scheme 9



With reference to Scheme 10 below, an alternative method of preparing intermediates of formula 3(a-1), wherein  $R^1$  is hydrogen, begins with an intermediate of formula 16 which can be converted to an intermediate of formula 19 using catalytic hydrogenation conditions, such as by using hydrogen gas and palladium on carbon in a reaction-inert, solvent such as tetrahydrofuran (THF). The intermediates of formula 19 can be converted into an intermediate of formula 20 by submitting the intermediate of formula 19 to an acetylation reaction, such as by treatment with the anhydride of a carboxylic acid (for example, acetic anhydride) in a reaction-inert solvent, such as toluene, and subsequent treatment with a base, such as potassium *tert*-butoxide, in a reaction-inert solvent, such as 1,2-dimethoxyethane. The

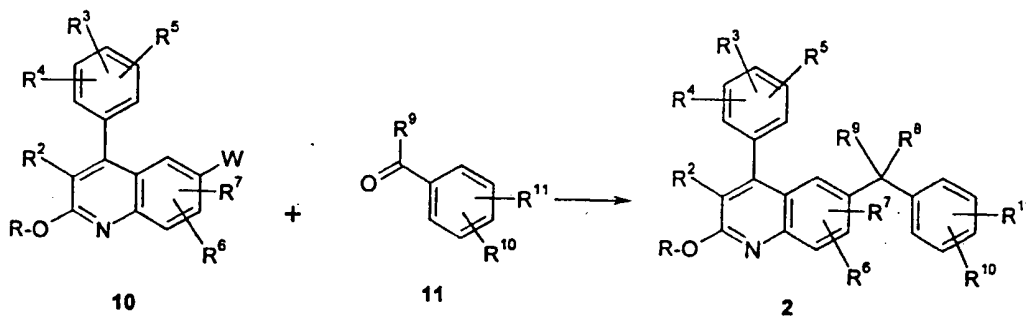
- 5 intermediate of formula 3(a-1) can be obtained by subjecting the intermediate of formula 20 to acidic conditions.

Scheme 10



- With reference to Scheme 11 below, the intermediate of formula 2, referred to above, may be prepared by reacting an intermediate of formula 10, wherein W is an appropriate leaving group, such as halo, with an intermediate ketone of formula 11. This reaction is done by converting the intermediate of formula 10 into an organometallic compound, by stirring it with a strong base such as butyl lithium, and subsequently adding the intermediate ketone of formula 11. Although this reaction gives at first instance a hydroxy derivative ( $\text{R}^8$  is hydroxy), said hydroxy derivative can be converted into other intermediates wherein  $\text{R}^8$  has another definition by performing functional group transformations familiar to those skilled in the art.

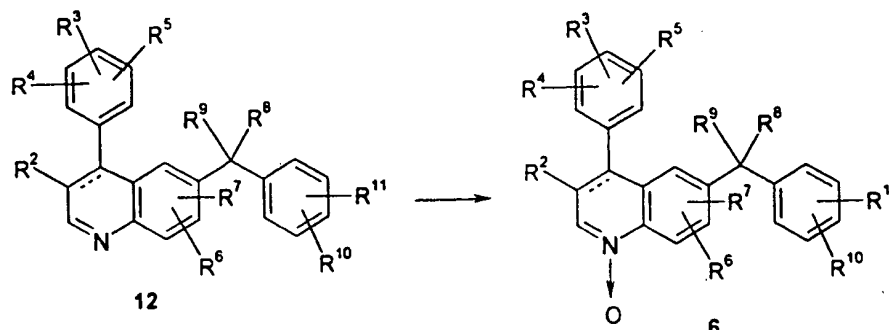
Scheme 11



- With reference to Scheme 12 below, the intermediate nitrones of formula 6 can be prepared by *N*-oxidizing a quinoline derivative of formula 12 with an appropriate oxidizing agent, such as *m*-chloro-peroxybenzoic acid or  $\text{H}_2\text{O}_2$ , in an appropriate solvent, such as dichloromethane.

5

Scheme 12

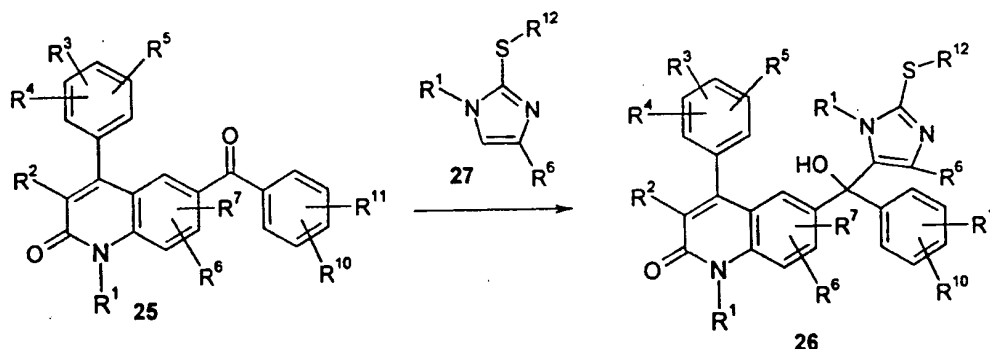


Said *N*-oxidation may also be carried out on a precursor of a quinoline of formula 12.

The intermediate of formula 12 may be metabolized *in vivo* into compounds of formula 1 via intermediates of formula 6. Hence, intermediates of formula 12 and 6 may act as prodrugs of compounds of formula 1. Such prodrugs are within the scope of the present invention.

With reference to Scheme 13 below, the compound of formula 26 can be prepared by reacting a compound of formula 25 with an intermediate of formula 27 where  $R^{12}$  is H or phenyl. This reaction requires the presence of a suitable base, such as *tert*-butyl lithium (when  $R^{12} = H$ ) or lithium 2,2,6,6-tetramethylpiperidine (when  $R^{12} = \text{phenyl}$ ), in an appropriate solvent, such as THF. The  $-SR^{12}$  group can be reductively removed from the compound of formula 26 with RANEY<sup>TM</sup> nickel or oxidatively with nitric acid or aqueous hydrogen peroxide in acetic acid.

Scheme 13



20

The compounds of formula 1 and some of the intermediates described above may have one or more stereogenic centers in their structure. Such stereogenic centers may be present in a *R* or a *S* configuration. Oxime moieties, such as where  $R^3, R^4, R^5, R^6$  or  $R^7$  is  $-\text{CH}=\text{NOR}^{12}$ , may exist in *E* or *Z* configurations.

The compounds of formula 1 as prepared in the above processes are generally racemic mixtures of enantiomers which can be separated from one another following

5 resolution procedures familiar to those skilled in the art. The racemic compounds of formula 1 may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula 1  
10 involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ  
15 enantiomerically pure starting materials.

The compounds of formula 1 that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula 1 from the reaction mixture as a pharmaceutically  
20 unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable  
25 organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is readily obtained. The desired acid addition salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid. Cationic salts of the compounds of formula 1 are similarly prepared except through reaction of a carboxy group with an appropriate cationic salt reagent, such as sodium,  
30 potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine, tromethamine, or diethanolamine.

The compounds of formula 1 and their pharmaceutically acceptable salts and solvates (hereinafter referred to, collectively, as "the therapeutic compounds") can be administered orally, transdermally (e.g., through the use of a patch), parenterally or topically. Oral administration is  
35 preferred. In general, compounds of the formula 1 and their pharmaceutically acceptable salts and solvates are most desirably administered in dosages ranging from about 1.0 mg up to about 500 mg per day, preferably from about 1 to about 100 mg per day in single or divided (i.e., multiple) doses. The therapeutic compounds will ordinarily be administered in daily dosages ranging from about 0.01 to about 10 mg per kg body weight per day, in single or divided doses.  
40 Variations may occur depending on the weight and condition of the person being treated and the particular route of administration chosen. In some instances, dosage levels below the lower limit

5 of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The therapeutic compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the two routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

Additionally, it is also possible to administer the therapeutic compounds topically and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The therapeutic compounds may also be administered to a mammal other than a human. The dosage to be administered to a mammal will depend on the animal species and the

5 disease or disorder being treated. The therapeutic compounds may be administered to animals in the form of a capsule, bolus, tablet or liquid drench. The therapeutic compounds may also be administered to animals by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. As an alternative the therapeutic compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

10 The compounds of formula 1 exhibit activity as Ras farnesylation inhibitors and are useful in the treatment of cancer and the inhibition of abnormal cell growth in mammals, including humans. The activity of the compounds of formula 1 as Ras farnesylation inhibitors may be determined by their ability, relative to a control, to inhibit Ras farnesyl transferase in vitro. This procedure is described below.

15 A crude preparation of human farnesyl transferase (FTase) comprising the cytosolic fraction of homogenized brain tissue is used for screening compounds in a 96-well assay format. The cytosolic fraction is prepared by homogenizing approx. 40 grams fresh tissue in 100 ml of sucrose/MgCl<sub>2</sub>/EDTA buffer (using a Dounce homogenizer; 10-15 strokes), centrifuging the homogenates at 1000 grams for 10 minutes at 4G, re-centrifuging the supernatant at 17,000 grams for 15 minutes at 4G, and then collecting the resulting supernatant. This supernatant is diluted to contain a final concentration of 50 mM Tris HCl (pH 7.5), 5 mM DTT, 0.2 M KCl, 20 mM ZnCl<sub>2</sub>, 1 mM PMSF and re-centrifuged at 178,000 grams for 90 minutes at 4G. The supernatant, termed "crude FTase" was assayed for protein concentration, aliquoted, and stored at -70°C.

25 The assay used to measure in vitro inhibition of human FTase is a modification of the method described by Amersham LifeScience for using their Farnesyl transferase (3H) Scintillation Proximity Assay (SPA) kit (TRKQ 7010). FTase enzyme activity is determined in a volume of 100 µl containing 50 mM N-(2-hydroxy ethyl) piperazine-N-(2-ethane sulfonic acid) (HEPES), pH 7.5, 30 mM MgCl<sub>2</sub>, 20 µM KCl, 5 mM Na<sub>2</sub>HPO<sub>4</sub>, 5 mM dithiothreitol (DTT), 0.01% Triton X-100, 5% dimethyl sulfoxide (DMSO), 20 µg of crude FTase, 0.12 mM [3H]-farnesyl pyrophosphate ([3H]-FPP; 36000 dpm/pmol, Amersham LifeScience), and 0.2 mM of biotinylated Ras peptide KTKCVIS (Bt-KTKCVIS) that is N-terminally biotinylated at its alpha amino group and was synthesized and purified by HPLC in house. The reaction is initiated by addition of the enzyme and terminated by addition of EDTA (supplied as the STOP reagent in kit TRKQ 7010) following a 45 minute incubation at 37°C. Prenylated and unprenylated Bt-KTKCVIS is captured by adding 10 µl of streptavidin-coated SPA beads (TRKQ 7010) per well and incubating the reaction mixture for 30 minutes at room temperature. The amount of radioactivity bound to the SPA beads is determined using a MicroBeta 1450 plate counter. Under these assay conditions, the enzyme activity is linear with respect to the concentrations of the prenyl group acceptor, Bt-KTKCVIS, and crude FTase, but saturating with respect to the prenyl donor, FPP. The assay reaction time is also in the linear range.

5 The test compounds are routinely dissolved in 100% dimethyl sulfoxide (DMSO). Inhibition of farnesyl transferase activity is determined by calculating percent incorporation of tritiated-farnesyl in the presence of the test compound vs. its incorporation in control wells (absence of inhibitor). IC<sub>50</sub> values, that is, the concentration required to produce half maximal farnesylation of Bt-KTKCVIS, is determined from the dose-responses obtained.

10 The following Examples further illustrate the invention. In the following Examples, "Et" refers to ethyl, "Me" refers to methyl, and "Ac" refers to acetyl.

#### EXAMPLE 1

6-[(4-Chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one

15 6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one (445 mg, 0.890 mMol), which was prepared following the procedures described in PCT international patent application publication number WO 97/21701 (published June 19, 1997), was dissolved in a solution of dichloromethane (DCM) (5.0 mL) and SOCl<sub>2</sub> (5.0 mL) under an atmosphere of dry N<sub>2</sub>. The reaction mixture was  
20 heated to 45°C and stirred overnight at this temperature. The reaction mixture was concentrated under vacuum and the residue was dissolved in anhydrous DMF (5.0 mL) under an atmosphere of dry N<sub>2</sub>. To this mixture was added potassium carbonate (674 mg, 4.88 mMol) and 1,2,4-triazole (168 mg, 2.44 mMol) and the mixture was heated to 80°C for 6 hours. The reaction mixture was concentrated under vacuum and partitioned between EtOAc  
25 and 0.01 N aqueous NaOH. The EtOAc layer was saved and washed 2 more times with 0.01 N aqueous NaOH and then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give 440 mg of a tan foam. The foam was chromatographed on flash silica gel eluting with MeOH/DCM/NH<sub>4</sub>OH (2/98/0.1) to give 264 mg of the titled compound.

C.I. m/z 551 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.03 (s, 1 H), 7.89 (s, 1 H), 7.60 (brs, 1 H),  
30 7.41 (d, J = 9.1 Hz, 1 H), 7.22-7.28 (m, 4 H), 7.16 (d, J = 2.3 Hz, 1 H), 6.92 (m, 3 H), 6.70 (s, 1 H), 6.67 (m, 2 H), 6.57 (s, 1 H), 3.99 (q, J = 6.9 Hz, 2 H), 3.76 (s, 3 H), 3.06 (s, 3 H), 1.42 (t, J = 6.9 Hz, 3 H).

#### EXAMPLE 2

6-[(4-Chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-4-(3-methoxy-phenyl)-1-methyl-1H-quinolin-2-one

35 The same procedure was used as described in example 1 except that 6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1-methyl-1H-quinolin-2-one, which was prepared following the procedures described in PCT international patent application publication number WO 97/21701 (published June 19, 1997), was used in  
40 the place of 6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one to give the titled compound.

- 5 C.I. m/z 537 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.01 (s, 1 H), 7.88 (s, 1 H), 7.51 (brs, 1 H), 7.39 (d, J = 8.9 Hz, 1 H), 7.22-7.26 (m, 4 H), 7.15 (d, J = 2.5 Hz, 1 H), 6.92 (m, 3 H), 6.68 (m, 3H), 6.53 (s, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.02 (s, 3 H).

### EXAMPLE 3

10 6-[(4-Chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

- The same procedure was used as described in example 1 except that 6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one, which was prepared following the procedures described in PCT international patent application publication number WO 97/21701 (published June 19, 1997), was used in the place of 6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one to give the titled compound.

C.I. m/z 541[M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.05 (s, 1 H), 7.89 (s, 1 H), 7.56 (s, 1 H), 7.38 (m, 2 H), 7.24-7.32 (m, 4 H), 7.16 (t, J = 1.6 Hz, 1 H), 7.04 (m, 2 H), 6.94 (d, J = 8.5 Hz, 2 H), 6.67 (m, 3H), 6.54 (s, 1 H), 3.75 (s, 3 H), 3.06 (s, 3 H).

20

### EXAMPLE 4

3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl]-benzaldehyde

- 4A. 5-[2-(4-Chloro-phenyl)-[1,3]dioxolan-2-yl]-3-(3-iodo-phenyl)-benzo[c]isoxazole  
2-(4-Chlorophenyl)-2-(4-nitrophenyl)-1,3-dioxolane (38.7 g, 127 mMol) was  
25 suspended in 190 mL of methanol (MeOH) under an atmosphere of dry N<sub>2</sub>. To this solution was added (3-iodophenyl)acetonitrile (46.3 g, 190 mMol) and 25.4 g (625 mMol) of sodium hydroxide (NaOH). The solution was then heated to reflux and reacted at this temperature for 2 hours. The reaction mixture was cooled to ambient temperature and the MeOH was removed under vacuum. The resulting red oil was partitioned between dichloromethane (DCM) and 0.1 N aqueous NaOH. The DCM layer was washed successively with 0.1 N  
30 aqueous NaOH and then brine. The DCM layer was dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum to give a dark red oil. The oil was stirred in MeOH and the titled compound precipitated out as a yellow solid. The yellow solid was washed with MeOH and dried under vacuum to give 52.4 g of the titled compound which was used without further  
35 purification.

4B. [6-Amino-3-(4-chloro-benzoyl)-cyclohexa-2,4-dienyl]-(3-iodo-phenyl)-methanone

- 5-[2-(4-Chloro-phenyl)-[1,3]dioxolan-2-yl]-3-(3-iodo-phenyl)-benzo[c]isoxazole (65.4 g, 130 mMol) was dissolved in a solution of tetrahydrofuran (THF) (500 mL) and DCM (100 mL).  
40 To this solution, was added 500 mL of titanium(III) chloride (10 wt.% solution in 20-30 wt. % hydrochloric acid (HCl)) and the reaction mixture was stirred for 1 hour. An additional 100 mL



5 of titanium(III) chloride (10 wt.% solution in 20-30 wt. % HCl) was added to the reaction mixture and the reaction mixture was stirred for 2.5 hours. The reaction mixture was then poured into ice water and the resulting heterogeneous solution was extracted with DCM. The DCM layer was successively washed with aqueous saturated  $\text{NaHCO}_3$  and brine. The DCM layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under vacuum to give titled compound  
10 as an orange oil (60 g). The oil was used without further purification.

4C. 6-(4-Chloro-benzoyl)-4-(3-iodo-phenyl)-1H-quinolin-2-one

[6-Amino-3-(4-chloro-benzoyl)-cyclohexa-2,4-dienyl]-(3-iodo-phenyl)-methan-one (60 g, 130 mMol) was dissolved in anhydrous toluene (450 mL) under an atmosphere of dry  $\text{N}_2$ . To this solution was added 180 mL of triethylamine ( $\text{NEt}_3$ ), 50 mL of acetic anhydride ( $\text{Ac}_2\text{O}$ )  
15 and 1.60 g (13.0 mMol) of 4-dimethylaminopyridine (DMAP). The reaction mixture was then heated to reflux and stirred at this temperature for 20 hours. The reaction mixture was cooled to ambient temperature and the precipitate was collected via suction filtration. The solid was washed with ethyl ether ( $\text{Et}_2\text{O}$ ) and dried under vacuum to give of the titled compound (63 g) which was used without further purification.

20 4D. 6-(4-Chloro-benzoyl)-4-(3-iodo-phenyl)-1-methyl-1H-quinolin-2-one

6-(4-Chloro-benzoyl)-4-(3-iodo-phenyl)-1H-quinolin-2-one (63 g, 130 mMol) was dissolved in THF (500 mL) under an atmosphere of dry  $\text{N}_2$ . To this solution, was added a 10 N aqueous  $\text{NaOH}$  (550 mL), benzyltriethylammonium chloride (13.8 g, 60.5 mMol) and methyl iodide (13.5 mL, 212.0 mMol). The reaction mixture was stirred at ambient temperature for 15  
25 hours after which time it was partitioned between DCM and water. The DCM layer was successively washed with water (4 times) and then brine. The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under vacuum to give 51.2 g of a yellow solid as the titled compound which was used without further purification.

4E. 6-(4-Chloro-benzoyl)-1-methyl-4-(3-vinyl-phenyl)-1H-quinolin-2-one

30 To a solution of 1,4-bis(diphenylphosphine)butane (120 mg, 0.28 mMol) in toluene (15 mL) was added dichlorobis(benzonitrile)palladium(II) (108 mg, 0.28 mMol) under an atmosphere of dry  $\text{N}_2$ . The reaction mixture was stirred at ambient temperature for 45 minutes after which time the solution was diluted with toluene (85 mL). To this solution was added 6-(4-chloro-benzoyl)-4-(3-iodo-phenyl)-1-methyl-1H-quinolin-2-one (14.0 g, 28.0 mMol)  
35 and tributyl(vinyl)tin (9.1 mL, 32.9 mMol). The reaction was heated to reflux and stirred at this temperature for 1 hour. The reaction mixture was concentrated under vacuum and chromatographed on flash silica gel eluting DCM until the tin impurities had eluted. The product was eluted off with DCM/MeOH (99:1) to give 9.61 g of the titled compound.

40 4F. 6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-2-phenylsulfanyl-3H-imidazol-4-yl)-methyl]-1-methyl-4-(3-vinyl-phenyl)-1H-quinolin-2-one

2,2,6,6-tetramethylpiperidine (4.5 mL, 26.5 mMol) was dissolved in a solution of anhydrous THF (100 mL) and anhydrous 1,2-dimethoxyethane (50 mL) under an atmosphere

5 of dry N<sub>2</sub> and the solution was then cooled to -78°C. To this solution was added 2.5 M n-butyllithium in hexanes (9.6 mL, 24.1 mMol) and the mixture was stirred for 20 minutes. To this solution was added 1-methyl-2-phenylthio-1-*H*-imidazole (4.58 g, 24.1 mMol) and the solution was stirred at -78°C for 45 minutes. 6-(4-Chloro-benzoyl)-1-methyl-4-(3-vinyl-phenyl)-1*H*-quinolin-2-one (9.64 g, 24.1 mMol) was then added and the solution was slowly warmed to  
10 ambient temperature and stirred overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the solution was partitioned between water and EtOAc. The aqueous layer was washed 2 more times with EtOAc. The EtOAc extracts were combined and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give a yellow oil. The oil was chromatographed on flash silica gel eluting with a gradient from EtOAc/hexanes (1:1) to  
15 EtOAc/hexanes (4:1) to give 8.66 g of the titled compound as a foam.

4G. 3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl]-benzaldehyde

6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-2-phenylsulfanyl-3*H*-imidazol-4-yl)-methyl]-1-methyl-4-(3-vinyl-phenyl)-1*H*-quinolin-2-one (8.66 g, 14.7 mMol) was dissolved in a solution of  
20 THF (40 mL) and water (35 mL). To this solution was added 4-methylmorpholine-*N*-oxide (4.12 g, 35.2 mMol) and 9.2 mL of osmium tetroxide (2.5% wt. solution in 2-methyl-2-propanol). Acetone was added to the mixture until it became homogeneous and the reaction mixture was then stirred overnight at ambient temperature. A white precipitate (5.0 g) formed overnight and was collected via suction filtration. The white precipitate was suspended in  
25 ethanol and RANEY™ Nickel (10 g) was added to the reaction mixture. The reaction was heated to reflux and stirred at this temperature for 2 hours. The reaction was filtered through CELITE™ and the CELITE™ was washed with copious amounts of ethanol. The ethanol filtrates were combined and concentrated under vacuum to give 2.59 g of a white solid. The white solid was suspended in THF (50 mL). To this solution was added a solution of sodium  
30 periodate (2.13 g, 10 mMol) in water (25 mL) and the reaction was stirred at ambient temperature for 2 hours. The solution was then partitioned between 0.01 N NaOH and DCM. The DCM was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give the titled compound as a waxy solid. The compound was used without further purification.

C.I. m/z 484 [M+1]; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 9.98 (s, 1 H), 7.97 (m, 1 H), 7.77 (m, 2 H),  
35 7.53-7.68 (m, 4 H), 7.14-7.27 (m, 5 H), 6.61 (s, 1 H), 6.12 (s, 1 H), 3.77 (s, 3 H), 3.39 (s, 3 H).

#### EXAMPLE 5

3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl]-benzaldehyde O-benzyl-oxime

3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3*H*-imidazol-4-yl)-methyl]-1-methyl-2-oxo-  
40 1,2-dihydro-quinolin-4-yl]-benzaldehyde (202 mg, 0.418 mMol) was dissolved in a solution of DCM (2.0 mL) and MeOH (2.0 mL) under an atmosphere of dry N<sub>2</sub>. To this solution was

- 5 added O-benzylhydroxylamine hydrochloride (66.8 mg, 418 mMol) and the mixture was stirred for 24 hours at ambient temperature. The reaction mixture was concentrated under vacuum and was purified by radial chromatography eluting with MeOH/EtOAc/NH<sub>4</sub>OH (5:95:0.1) to give the titled compound as an oil.

C.I. m/z 589 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 (s, 1 H), 7.58 (dd, J = 1.7, 8.8 Hz, 1 H),  
10 7.51 (d, J = 8.8 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 2 H), 7.05-7.33 (m, 13 H), 6.48 (s, 1 H), 6.12 (brs, 1 H), 5.16 (s, 2 H), 3.58 (s, 3 H), 3.27 (s, 3 H).

#### EXAMPLE 6

3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl]-benzaldehyde O-methyl-oxime

- 15 The procedure was used as described in example 5 except that O-methylhydroxylamine hydrochloride was used in the place of O-benzylhydroxylamine hydrochloride to give the titled compound.

C.I. m/z 513 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.00 (s, 1 H), 7.57 (m, 2 H), 7.46 (brs, 1 H),  
20 7.14-7.38 (m, 9 H), 6.61 (s, 1 H), 6.25 (brs, 1 H), 3.95 (s, 3 H), 3.69 (s, 3 H), 3.34 (s, 3 H).

#### EXAMPLE 7

3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl]-benzaldehyde O-ethyl-oxime

- 25 The procedure was used as described in example 5 except that O-ethylhydroxylamine hydrochloride was used in the place of O-benzylhydroxylamine hydrochloride to give the titled compound.

C.I. m/z 527 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.96 (s, 1 H), 7.57 (d, J = 2.1, 8.9 Hz, 1 H),  
7.53 (d, J = 8.9 Hz, 1 H), 7.41 (brs, 1 H), 7.07-7.33 (m, 9 H), 6.52 (s, 1 H), 6.13 (brs, 1 H),  
4.19 (q, J = 7.1 Hz, 2 H), 3.62 (s, 3 H), 3.30 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H).

#### EXAMPLE 8

- 30 3-[6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl]-benzaldehyde O-tert-butyl-oxime

The procedure was used as described in example 5 except that O-tert-butylhydroxylamine hydrochloride was used in the place of O-benzylhydroxylamine hydrochloride to give the titled compound.

- 35 C.I. m/z 555 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.91 (s, 1 H), 7.53 (m, 2 H), 7.38 (brs, 1 H), 7.15-7.32 (m, 7 H), 7.03 (brs, 1 H), 6.96 (m, 1 H), 6.46 (s, 1 H), 6.06 (s, 1 H), 3.57 (s, 3 H), 3.26 (s, 3 H), 1.28 (s, 9 H).

5

EXAMPLE 9

3-{6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl}-benzaldehyde O-allyl-oxime

The procedure was used as described in example 5 except that O-allylhydroxylamine hydrochloride was used in the place of O-benzylhydroxylamine hydrochloride to give the titled compound.

C.I. m/z 539 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.98 (s, 1 H), 7.58 (dd, J = 1.5 Hz, 8.9 Hz, 1 H), 7.50 (d, J = 7.9 Hz, 1 H), 7.37 (brs, 1 H), 7.00-7.32 (m, 9 H), 6.43 (s, 1 H), 6.06 (s, 1 H), 5.99 (m, 1 H), 5.25 (m, 2 H), 4.60 (d, J = 5.8 Hz, 2 H), 3.56 (s, 3 H), 3.28 (s, 3 H).

EXAMPLE 10

3-{6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl}-benzaldehyde oxime

The procedure was used as described in example 5 except that hydroxylamine hydrochloride was used in the place of O-benzylhydroxylamine hydrochloride to give the titled compound.

C.I. m/z 499 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.01 (s, 1 H), 7.58 (m, 2 H), 7.41 (brs, 1 H), 7.36 (d, J = 7.3 Hz, 1 H), 7.16-7.30 (m, 7 H), 7.04 (d, J = 7.3 Hz, 1 H), 6.44 (s, 1 H), 6.21 (s, 1 H), 3.52 (s, 3 H), 3.31 (s, 3 H).

EXAMPLE 11

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

11A. 6-(4-Chloro-benzoyl)-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

A solution of 6-(4-Chloro-benzoyl)-4-(3-chloro-phenyl)-1H-quinolin-2-one (3.10 g; 7.87 mmol), prepared according to the methods described in PCT international patent application publication number WO 97/21701 (published June 19, 1997), in DMF (28 mL) was treated with cesium carbonate (2.56 g, 7.87 mmol) and (bromomethyl)cyclopropane (2.13 g, 15.7 mmol). The reaction mixture was stirred at room temperature for 12 hours, diluted with dichloromethane (25 mL), and washed with 1N HCl (2 x 10 mL) and brine (20 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give a black residue. Purification by flash column chromatography (silica, ethyl acetate:petroleum ether 1:9 - 3:7) gave 6-(4-Chloro-benzoyl)-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (2.39 g, 68%) as an off-white foam.

C.I. m/z 448 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 8.01 (dd, J = 8.9, 2.1 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.69-7.59 (m, 3H), 7.44-7.34 (m, 5H), 7.28-7.24 (m, 1H), 6.66 (s, 1H), 4.29 (d, J = 6.9 Hz, 2H), 1.31-1.23 (m, 1H), 0.60-0.51 (m, 4H).

5           11B.   4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

A solution of 2-(tert-Butyl-dimethyl-silanyl)-1-methyl-1H-imidazole (1.61 g, 8.2 mmol) in THF (40 mL) at -78°C was treated with sec-butyllithium (1.3 M in cyclohexane, 7.9 mL, 10.3 mmol). The reaction mixture was warmed to 0°C, stirred for 3 hours, and cooled to -78°C. A solution of 6-(4-Chloro-benzoyl)-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (2.87 g, 6.4 mmol) in THF (20 mL) was cannulated into the reaction mixture, slowly warmed to room temperature, and stirred overnight. The reaction mixture was quenched with ammonium chloride (12 mL), diluted with ether (200 mL), and washed with H<sub>2</sub>O (200 mL) and brine (200 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to give 6-[[2-(tert-butyl-dimethyl-silanyl)-3-methyl-3H-imidazol-4-yl]-(4-chloro-phenyl)-hydroxy-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (4.35 g) as a yellow foam. The crude material was used in the next step without any further purification.

A solution of 6-[[2-(tert-butyl-dimethyl-silanyl)-3-methyl-3H-imidazol-4-yl]-(4-chloro-phenyl)-hydroxy-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (4.24 g crude) in THF (100 mL) was treated with tetrabutylammonium chloride (1 M in THF, 10.0 mmol). The reaction mixture was stirred at room temperature for 12 hours, poured into H<sub>2</sub>O (200 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with 1N HCl (100 mL), aqueous NaHCO<sub>3</sub> (100 mL), and brine (100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give a light green foam. Purification by flash column chromatography (silica, EtOAc:pet. ether:NH<sub>4</sub>OH 1:1:0.01) gave 4-(3-Chloro-phenyl)-6-[[4-(chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (2.3 g, 68%) as a light yellow solid.

C.I. m/z 530 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.60 (dd, J = 9.13, 2.2 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.38 (dd, J = 2.1, 1.0 Hz, 1H), 7.36-7.15 (m, 8H), 7.03 (d, J = 7.7 Hz, 1H), 6.56 (s, 1H), 6.24 (s, 1H), 4.25-4.20 (m, 2H), 3.34 (s, 3H), 1.27-1.22 (m, 1H), 0.59-0.50 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 162.0, 149.0, 142.5, 139.9, 136.0, 134.5, 133.7, 130.0, 129.9, 128.9, 128.7, 128.4, 128.2, 126.9, 125.7, 121.7, 114.8, 46.1, 33.5, 9.9, 4.1.

**EXAMPLE 12**

35           6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

A solution of 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (2.3 g, 4.35 mmol) in dichloromethane (60 mL) at 0°C was treated with thionyl chloride (15 mL). The reaction mixture was warmed to room temperature, stirred for 1 hour, heated to 45°C, and stirred for an additional hour. The mixture was cooled to ambient temperature and concentrated *in vacuo* to give 6-[Chloro-(4-

5 chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one; hydrochloride (2.15 g, 85%) as a bright yellow powder.

A solution of 6-[Chloro-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one; hydrochloride (2.15 g, 3.7 mmol) in THF (40 mL) was treated with ammonium, stirred at ambient temperature for 2 hours, and concentrated in vacuo. The reaction mixture was diluted with ethyl acetate/H<sub>2</sub>O (1:1, 200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give a crude yellow foam. Purification by flash column chromatography (silica, EtOAc:MeOH:NEt<sub>3</sub> 9:1:0.1) gave 6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (1.54 g, 79%) as a yellow foam.

C.I. m/z 529 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.58-7.52 (m, 2H), 7.40-7.39 (m, 2H), 7.38 (dd, J = 2.1, 1.2 Hz, 1H), 7.33-7.21 (m, 3H), 7.10-7.04 (m, 4H), 6.63 (s, 1H), 6.31 (s, 1H), 4.28 (d, J = 6.8 Hz, 2H), 3.39 (s, 3H), 2.24 (s, 2H), 1.30-1.22 (m, 1H), 0.62-0.52 (m, 4H).

Separation of the Enantiomers of 6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (0.68 g) was separated into its enantiomers and purified by high-performance liquid chromatography over CHIRALCEL™ OD (manufactured by Daicel Chemical Industries, LTD, Osaka, Japan) (20 μm; eluent: hexane/isopropanol/diethylamine 60/40/0.1; 25°C). Under these conditions, 0.21 g of the faster eluting enantiomer A was obtained and 0.20 g of the slower moving enantiomer B. Both enantiomers were >97% optically pure.

### EXAMPLE 13

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,3]triazol-2-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one and 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,3]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

A solution of 6-[Chloro-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (0.094 g, 0.17 mmol) in DMF (7 mL) was treated with K<sub>2</sub>CO<sub>3</sub> (0.24 g, 0.17 mmol) and 1,2,3-triazole (0.061 mL, 1.03 mmol). The reaction mixture was heated at 80°C for 12 hours, diluted with H<sub>2</sub>O (2 mL), and extracted with EtOAc (2 mL). The organic phase was washed with brine (2 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated *in vacuo* to give a yellow oil. Purification by radio chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:NH<sub>4</sub>OH 98:1.8:0.2) gave 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,3]triazol-2-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (34 mg, 34%) and 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,3]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (9.5 mg, 9%) as yellow oils.

5 C.I. m/z 581 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.74 (s, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.51 (d, J = 8.9 Hz, 1H), 7.38-7.05 (m, 7H), 6.98-6.95 (m, 3H), 6.63 (s, 1H), 6.42 (s, 1H), 4.25 (d, J = 6.9 Hz, 2H), 3.09 (s, 3H), 1.29-1.25 (m, 1H), 0.58-0.51 (m, 4H).

C.I. m/z 581 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.76 (s, 1H), 7.56-7.52 (m, 2H), 7.41-7.25 (m, 6H), 7.16 (s, 1H), 7.06-7.04 (m, 1H), 6.92-6.90 (m, 3H), 6.66 (s, 1H), 6.57 (s, 1H), 4.26 (d, J = 6.6 Hz, 2H), 3.06 (s, 3H), 1.30-1.24 (m, 1H), 0.59-0.55 (m, 4H).

#### EXAMPLE 14

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The same procedure that was used in example 13 was followed except except 1,2,4-triazole was used in place of 1,2,3-triazole to give 4-(3-chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (8.2 mg, 8%) as a yellow solid.

C.I. m/z 581 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 8.06 (s, 1H), 7.90 (s, 1H), 7.56 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 2.0, 1.1 Hz, 1H), 7.32-7.24 (m, 4H), 7.17 (s, 1H), 7.06-6.95 (m, 4H), 6.66 (s, 1H), 6.55 (s, 1H), 4.27 (d, J = 6.8 Hz, 2H), 3.07 (s, 3H), 1.30-1.23 (m, 1H), 0.61-0.52 (m, 4H).

Separation of the Enantiomers of 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one was separated into its enantiomers and purified by high-performance liquid chromatography over CHIRALPAK™ AD (manufactured by Daicel Chemical Industries, LTD, Osaka, Japan) (20 μm; eluent: hexane/isopropanol/diethylamine 75/25/0.1; 25°C). Both enantiomers were >97% optically pure.

#### EXAMPLE 15

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-pyrrolidin-1-yl-methyl]-1-methyl-1H-quinolin-2-one

The same procedure that was used in example 13 was followed except except pyrrolidine was used in place of 1,2,3-triazole to give 4-(3-chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-pyrrolidin-1-yl-methyl]-1-methyl-1H-quinolin-2-one (35.3 mg, 35%) as a yellow solid.

C.I. m/z 583 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.56-7.30 (m, 6H), 7.25-7.20 (m, 6H), 6.86 (s, 1H), 6.66 (s, 1H), 4.26 (d, J = 6.9 Hz, 2H), 3.38 (s, 3H), 2.23-2.20 (m, 4H), 1.61-1.49 (m, 4H), 1.31-1.24 (m, 1H), 0.62-0.52 (m, 4H).

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EXAMPLE 16

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-(4-methyl-piperazin-1-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one; hydrochloride

The same procedure that was used in example 13 was followed except except N-methyl piperzine was used in place of 1,2,3-triazole to give 4-(3-chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-(4-methyl-piperazin-1-yl)-methyl]-1-methyl-1H-quinolin-2-one (17.5 mg) as a yellow solid.

C.I. m/z 612 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.50-7.20 (m, 12H), 6.85 (s, 1H), 6.67 (s, 1H), 4.25 (d, J = 6.6 Hz, 2H), 3.44 (s, 3H), 2.86-2.03 (m, 8H), 2.19 (s, 3H), 1.37-1.24 (m, 1H), 0.61-0.52 (m, 4H).

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EXAMPLE 17

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-piperidin-1-yl-methyl]-1-methyl-1H-quinolin-2-one

The same procedure that was used in example 13 was followed except except piperidine was used in place of 1,2,3-triazole to give 4-(3-chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-piperidin-1-yl-methyl]-1-methyl-1H-quinolin-2-one (31.3 mg, 31%) as a yellow foam.

C.I. m/z 597 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.87-7.24 (br.m, 12H), 6.78 (br.s, 1H), 6.65 (s, 1H), 4.24 (br.s, 2H), 3.45 (br.s, 3H), 1.70-1.18 (m, 9H), 0.93-0.88 (m, 2H), 0.58-0.55 (m, 4H).

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EXAMPLE 18

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-pyrazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The same procedure that was used in example 13 was followed except except pyrazole was used in place of 1,2,3-triazole to give 4-(3-chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-pyrazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (29.6 mg, 30%) as a yellow oil.

C.I. m/z 580 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.62 (s, 1H), 7.51-7.48 (m, 2H), 7.38-7.36 (m, 1H), 7.30-7.21 (m, 5H), 7.16 (s, 1H), 7.07 (d, J = 1.0 Hz, 1H), 7.05-6.97 (m, 3H), 6.63 (s, 1H), 6.53 (s, 1H), 6.30 (dd, J = 2.9, 1.2 Hz, 1H), 4.25 (d, J = 7.1 Hz, 2H), 3.00 (s, 3H), 1.29-1.23 (m, 1H), 0.59-0.50 (m, 4H).

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EXAMPLE 19

4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-morpholin-4-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one; hydrochloride

The same procedure that was used in example 13 was followed except except morpholine was used in place of 1,2,3-triazole to give 4-(3-chloro-phenyl)-6-[(4-chloro-phenyl)-

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- 5 (3-methyl-3H-imidazol-4-yl)-morpholin-4-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one  
(53.1 mg) as a yellow solid.

C.I. m/z 599 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.60-7.10 (m, 12H), 6.89 (s, 1H), 6.68 (s, 1H), 4.27 (d, J = 6.2 Hz, 2H), 3.68 (br.s, 4H), 3.42 (br.s, 3H), 2.39 (br.s, 4H), 1.29 (br.s, 1H), 0.60-0.55 (m, 4H).

#### EXAMPLE 20

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4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-cyclopropylamino-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

- The same procedure that was used in example 13 was followed except cyclopropyl amine was used in place of 1,2,3-triazole to give 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-cyclopropylamino-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one  
15 (20.4 mg, 38%) as a yellow solid.

C.I. m/z 569 [M+1]; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.64 (dd, J = 8.9, 2.1 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.42-7.33 (m, 4H), 7.28-7.15 (m, 6H), 6.72 (s, 1H), 6.62 (s, 1H), 4.25 (d, J = 6.8 Hz, 2H), 3.27 (s, 3H), 1.90-1.89 (m, 1H), 1.27-1.23 (m, 1H), 0.58-0.52 (m, 4H), 0.31-0.14 (m,

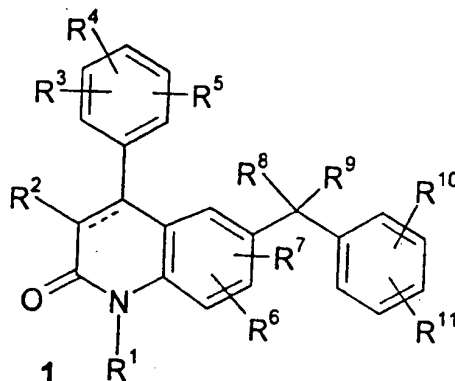
20 4H).

5

CLAIMS

What is claimed is:

1. A compound of the formula 1



or a pharmaceutically acceptable salt, prodrug or solvate thereof wherein:

- 10 the dashed line indicates that the bond between C-3 and C-4 of the quinolin-2-one ring is a single or double bond;

- 15  $R^1$  is selected from H,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{13}R^{14})_qC(O)R^{12}$ ,  $-(CR^{13}R^{14})_qC(O)OR^{15}$ ,  $-(CR^{13}R^{14})_qOR^{12}$ ,  $-(CR^{13}R^{14})_qSO_2R^{15}$ ,  $-(CR^{13}R^{14})_t(C_3-C_{10}$  cycloalkyl),  $-(CR^{13}R^{14})_t(C_6-C_{10}$  aryl), and  $-(CR^{13}R^{14})_t(4-10$  membered heterocyclic), wherein  $t$  is an integer from 0 to 5 and  $q$  is an integer from 1 to 5, said cycloalkyl, aryl and heterocyclic  $R^1$  groups are optionally fused to a  $C_6-C_{10}$  aryl group, a  $C_5-C_8$  saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing  $R^1$  groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4  $R^6$  groups;

- 20  $R^2$  is halo, cyano,  $-C(O)OR^{15}$ , or a group selected from the substituents provided in the definition of  $R^{12}$ ;

- 25 each  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  is independently selected from H,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido,  $-OR^{12}$ ,  $-C(O)R^{12}$ ,  $-C(O)OR^{12}$ ,  $-NR^{13}C(O)OR^{15}$ ,  $-OC(O)R^{12}$ ,  $-NR^{13}SO_2R^{15}$ ,  $-SO_2NR^{12}R^{13}$ ,  $-NR^{13}C(O)R^{12}$ ,  $-C(O)NR^{12}R^{13}$ ,  $-NR^{12}R^{13}$ ,  $-CH=NOR^{12}$ ,  $-S(O)_jR^{12}$  wherein  $j$  is an integer from 0 to 2,  $-(CR^{13}R^{14})_t(C_6-C_{10}$  aryl),  $-(CR^{13}R^{14})_t(4-10$  membered heterocyclic), and  $-(CR^{13}R^{14})_t(C_3-C_{10}$  cycloalkyl), and wherein in the foregoing  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  groups  $t$  is an integer from 0 to 5; the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a  $C_6-C_{10}$  aryl group, a  $C_5-C_8$  saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido,  $-NR^{13}SO_2R^{15}$ ,  $-SO_2NR^{12}R^{13}$ ,  $-C(O)R^{12}$ ,  $-C(O)OR^{12}$ ,  $-OC(O)R^{12}$ ,  $-NR^{13}C(O)OR^{15}$ ,  $-NR^{13}C(O)R^{12}$ ,  $-C(O)NR^{12}R^{13}$ ,  $-NR^{12}R^{13}$ ,  $-OR^{12}$ ,  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,
- 30

5  $-(CR^{13}R^{14})_t(C_6-C_{10} \text{ aryl})$ , and  $-(CR^{13}R^{14})_t(4-10 \text{ membered heterocyclic})$ , wherein  $t$  is an integer from 0 to 5;

$R^8$  is H,  $-OR^{12}$ ,  $-NR^{12}R^{13}$ ,  $-NR^{12}C(O)R^{13}$ , cyano,  $-C(O)OR^{13}$ ,  $-SR^{12}$ ,  $-(CR^{13}R^{14})_t(4-10 \text{ membered heterocyclic})$ , wherein  $t$  is an integer from 0 to 5, or  $C_1-C_6$  alkyl, wherein said heterocyclic and alkyl moieties are optionally substituted by 1 to 3  $R^6$  substituents;

10  $R^9$  is  $-(CR^{13}R^{14})_t(\text{imidazolyl})$  wherein  $t$  is an integer from 0 to 5 and said imidazolyl moiety is optionally substituted by 1 or 2  $R^6$  substituents;

each  $R^{10}$  and  $R^{11}$  is independently selected from the substituents provided in the definition of  $R^6$ ;

each  $R^{12}$  is independently selected from H,  $C_1-C_{10}$  alkyl,  $C_2-C_{10}$  alkenyl,   
15  $-(CR^{13}R^{14})_t(C_3-C_{10} \text{ cycloalkyl})$ ,  $-(CR^{13}R^{14})_t(C_6-C_{10} \text{ aryl})$ , and  $-(CR^{13}R^{14})_t(4-10 \text{ membered heterocyclic})$ , wherein  $t$  is an integer from 0 to 5; said cycloalkyl, aryl and heterocyclic  $R^{12}$  groups are optionally fused to a  $C_6-C_{10}$  aryl group, a  $C_5-C_8$  saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing  $R^{12}$  substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro,   
20 trifluoromethyl, trifluoromethoxy, azido,  $-C(O)R^{13}$ ,  $-C(O)OR^{13}$ ,  $-OC(O)R^{13}$ ,  $-NR^{13}C(O)R^{14}$ ,  $-C(O)NR^{13}R^{14}$ ,  $-NR^{13}R^{14}$ , hydroxy,  $C_1-C_6$  alkyl,  $C_2-C_{10}$  alkenyl and  $C_1-C_6$  alkoxy;

each  $R^{13}$  and  $R^{14}$  is independently H or  $C_1-C_6$  alkyl, and where  $R^{13}$  and  $R^{14}$  are as  $-(CR^{13}R^{14})_q$  or  $(CR^{13}R^{14})_t$ , each is independently defined for each iteration of  $q$  or  $t$  in excess of 1;

25  $R^{15}$  is selected from the substituents provided in the definition of  $R^{12}$  except  $R^{15}$  is not H; and,

provided that where  $R^1$  is not  $-(CR^{13}R^{14})_t(C_3-C_{10} \text{ cycloalkyl})$ , wherein  $t$  is an integer from 0 to 5, optionally substituted as provided in the definition of  $R^1$  above, then  $R^8$  is triazolyl optionally substituted by 1 or 2  $R^6$  groups, or at least one of  $R^3$ ,  $R^4$  and  $R^5$  is  $-CH=NOR^{12}$  or   
30  $-S(O)_jR^{12}$  wherein  $j$  is an integer from 0 to 2 and  $R^{12}$  is as defined above.

2. A compound according to claim 1 wherein  $R^3$  is  $-CH=NOR^{12}$ .

3. A compound according to claim 2 wherein  $R^1$  is H,  $C_1-C_6$  alkyl, or cyclopropylmethyl;  $R^2$  is H; and  $R^8$  is  $-NR^{12}R^{13}$ ,  $-OR^{12}$ , or a heterocyclic group selected from triazolyl, imidazolyl, pyrazolyl, and piperidinyl, wherein said heterocyclic group is optionally   
35 substituted by an  $R^6$  group.

4. A compound according to claim 1 wherein  $R^1$  is cyclopropylmethyl.

5. A compound according to claim 4 wherein  $R^2$  is H; and  $R^8$  is  $-NR^{12}R^{13}$ ,  $-OR^{12}$ , or a heterocyclic group selected from triazolyl, imidazolyl, pyrazolyl, and piperidinyl, wherein said heterocyclic group is optionally substituted by an  $R^6$  group.

40 6. A compound according to claim 1 wherein  $R^8$  is triazolyl optionally substituted by an  $R^6$  group.

- 5        7. A compound according to claim 6 wherein R<sup>1</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, or cyclopropylmethyl; R<sup>2</sup> is H; R<sup>9</sup> is imidazolyl optionally substituted by C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>4</sup>, R<sup>5</sup>, R<sup>10</sup> and R<sup>11</sup> are each independently selected from H and halo.
8. A compound according to claim 1 wherein said compound is selected from the group consisting of:
- 10        3-{6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl}-benzaldehyde O-methyl-oxime;
- 3-{6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl}-benzaldehyde O-ethyl-oxime;
- 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-
- 15        1-cyclopropylmethyl-1H-quinolin-2-one;
- 6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;
- 4-(3-Chloro-phenyl)-6-[(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-[1,2,4]triazol-1-yl-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one;
- 20        and the pharmaceutically acceptable salts, prodrugs and solvates of the foregoing compounds.
9. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound according to claim 1 that is effective in inhibiting farnesyl protein transferase.
- 25        10. A according to claim 9 wherein said abnormal cell growth is cancer.
11. A method according to claim 10 wherein said cancer comprises lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma
- 30        of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the
- 35        kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of two or more of the foregoing cancers.
12. A method according to claim 9 wherein said abnormal cell growth is a benign proliferative disease.
- 40        13. A method according to claim 12 wherein said benign proliferative disease comprises psoriasis, benign prostatic hypertrophy, or restinosis.

- 5           14. A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound according to claim 1 in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-  
10 hormones, and anti-androgens.
15. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound according to claim 1 that is effective in treating abnormal cell growth.
16. A pharmaceutical composition for the treatment of abnormal cell growth in a  
15 mammal which comprises an amount of a compound according to claim 1 that is effective in inhibiting farnesyl protein transferase and a pharmaceutically acceptable carrier.
17. A pharmaceutical composition according to claim 16 wherein said abnormal cell growth is cancer.
18. A pharmaceutical composition according to claim 17 wherein said cancer comprises  
20 lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small  
25 intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors,  
30 brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.
19. A pharmaceutical composition according to claim 16 wherein said abnormal cell growth is a benign proliferative disease.
20. A pharmaceutical composition according to claim 19 wherein said benign proliferative disease comprises psoriasis, benign prostatic hypertrophy, or restinosis.
- 35           21. A pharmaceutical composition for the treatment of abnormal cell growth in a mammal which comprises an amount of a compound according to claim 1 that is effective in treating abnormal cell growth and a pharmaceutically acceptable carrier.
22. A pharmaceutical composition for the treatment of abnormal cell growth in a  
40 mammal which comprises a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating

- 5 antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.
23. A method for the treatment of an infection in a mammal, wherein said infection is facilitated by farnesyl protein transferase, which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1.
- 10 24. The method of claim 23 wherein said infection is hepatitis delta virus or malaria.
25. A pharmaceutical composition for the treatment of an infection in a mammal, wherein said infection is facilitated by farnesyl protein transferase, which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
- 15 26. The pharmaceutical composition of claim 25 wherein said infection is hepatitis delta virus or malaria.

# INTERNATIONAL SEARCH REPORT

Inte Application No  
PCT/IB 99/01393

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D401/06 C07D401/14 A61K31/4704

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 21701 A (JANSSEN PHARMACEUTICA NV ; VENET MARC GASTON (FR); ANGIBAUD PATRICK) 19 June 1997 (1997-06-19) claims	1-26
Y	WO 97 16443 A (JANSSEN PHARMACEUTICA NV ; END DAVID WILLIAM (US); VENET MARC GASTO) 9 May 1997 (1997-05-09) claims	1-26
A	EP 0 371 564 A (JANSSEN PHARMACEUTICA NV) 6 June 1990 (1990-06-06) claims	1-26
P, Y	WO 98 55124 A (JANSSEN PHARMACEUTICA NV ; END DAVID WILLIAM (US); ZELESKO MICHAEL) 10 December 1998 (1998-12-10) claims	1-26
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "G" document member of the same patent family

Date of the actual completion of the international search

21 October 1999

Date of mailing of the international search report

08/11/1999

Name and mailing address of the ISA

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Chouly, J

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 99/01393

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	<p>WO 98 40383 A (JANSSEN PHARMACEUTICA NV ;ANGIBAUD PATRICK RENE (FR); LIGNY YANNIC) 17 September 1998 (1998-09-17) claims</p> <p>-----</p>	1-26



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/ 01393

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-15, 23-24  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 9-15, 23-24  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/01393

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9721701	A	19-06-1997	AU 7294896 A	03-07-1997
			BG 102458 A	30-06-1999
			CN 1203598 A	30-12-1998
			CZ 9801573 A	14-10-1998
			EP 0865440 A	23-09-1998
			HR 960576 A	28-02-1998
			HU 9900185 A	28-04-1999
			JP 10511405 T	04-11-1998
			NO 980927 A	08-06-1998
			NZ 320244 A	29-06-1999
			PL 325962 A	17-08-1998
			SK 70498 A	07-10-1998
WO 9716443	A	09-05-1997	AU 7493396 A	22-05-1997
			CN 1200732 A	02-12-1998
			CZ 9801272 A	16-12-1998
			NO 980928 A	29-04-1998
			NZ 321576 A	28-05-1999
			PL 328230 A	18-01-1999
			SK 55698 A	11-02-1999
EP 0371564	A	06-06-1990	AT 124941 T	15-07-1995
			AU 620946 B	27-02-1992
			AU 4564689 A	07-06-1990
			CA 2002864 A	29-05-1990
			CN 1042912 A,B	13-06-1990
			CN 1106004 A,B	02-08-1995
			CN 1106005 A,B	02-08-1995
			CY 1920 A	07-03-1997
			DE 68923430 D	17-08-1995
			DK 599489 A	30-05-1990
			ES 2088889 T	01-10-1996
			FI 101964 B	30-09-1998
			GR 3017351 T	31-12-1995
			HK 118196 A	12-07-1996
			HU 9500329 A	30-10-1995
			IE 67803 B	01-05-1996
			JP 2223579 A	05-09-1990
			JP 2916181 B	05-07-1999
			NO 174509 B	07-02-1994
			NZ 231441 A	28-05-1991
			PT 92448 A,B	31-05-1990
			SU 1780536 A	07-12-1992
			US 5037829 A	06-08-1991
			ZM 4289 A	29-06-1990
			ZW 15889 A	17-07-1991
			US 5441954 A	15-08-1995
			US 5612354 A	18-03-1997
			US 5185346 A	09-02-1993
			US 5268380 A	07-12-1993
			US 5028606 A	02-07-1991
			US 5151421 A	29-09-1992
WO 9855124	A	10-12-1998	AU 8020798 A	21-12-1998
WO 9840383	A	17-09-1998	AU 7031898 A	29-09-1998